Serial Number: 10/679,987
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REMARKS

Upon entry of the foregoing amendment, Claims 1-3, 7-14 and 18-22 will be pending in the instant application. Claims 1, 2, 12 and 13 are amended in this response. Each amendment has written support in the application. For example, the amendment to Claims 1 and 12 are supported by Claims 2 and 13 as originally filed. The amendment to Claims 2 and 13 merely deletes the limitation that has been incorporated into amended Claims 1 and 12, respectively. Accordingly, no new matter has been added to the application. Reconsideration of the amended claims in view of the following remarks is respectfully requested.

Rejections Under 35 U.S.C. § 102

Claims 1, 9-12 and 20-22 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Karamohamed *et al.*, Biotechniques 24:302-306 (1999) (hereinafter "Karamohamed"). This rejection should be withdrawn because Karamohamed does not anticipate the amended claims.

In order to anticipate a claim, a cited reference must teach every element of the claim (see Verdegaal Bros. v. Union Oil Co of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Claims 1 and 12 have been amended to describe methods for detecting the activity of an RNA-dependent RNA polymerase, or "RdRp". Karamohamed teaches methods for detecting the activity of reverse transcriptase, a DNA polymerase. Since the methods of Karamohamed do not detect the activity of an RNA polymerase, Karamohamed does not anticipate amended claims 1 or 12. Claims 9-10 and, 20-22, all of which are dependent on either claim 1 or 12 and are therefore also directed to an RdRp assay, are also free from Karamohomed. Withdrawl of the 102(b) rejection is respectfully requested.

Rejections Under 35 U.S.C. § 103

Claims 2-3, 7-8, 13-14 and 17-19 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Karamohamed in view of Lohmann *et al.*, J. Viral. Hepatitis 7:167-74 (2000) (hereinafter "Lohmann"). As noted previously, Karamohamed describes a method for detecting the activity of a DNA polymerase. Lohmann describes the evaluation of Hepatitis C virus NS5B activity. The Examiner alleges that it would have been obvious to one of ordinary skill in the art to have tested the RNA polymerase of Lohmann using the method described in Karamohamed. Applicants disagree.

One skilled in the art, with the disclosures of Karamohamed and Lohmann in hand, would not have had a reasonable expectation that RNA polymerase activity could be detected in an assay designed to measure the activity of a DNA polymerase. More specifically, one skilled in the art would not have expected substitution of the RNA forms of the nucleotide triphospiates (NTPs) needed for an RNA polymerase assay for the DNA forms of the NTPs described in Karamohamed to work in a luciferase-based assay.

While obviousness does not require absolute predictability, at least some degree of predictability is required. In re Rinehart, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976). As will be detailed below, one skilled in the art would not have been able to predict whether the combination of teachings suggested by the Examiner would have resulted in a sensitive and continuous RdRp assay in which activity is measured by a system based on the detection of ATP by luciferase.

As noted previously, Karamohamed describes an assay which measures the activity of the DNA polymerase reverse transcriptase (RT). In the first reaction of Karamohamed's assay, a primer and template are combined with RT before the reaction is started by addition of deoxynucleotides (see Karamohamed p. 304, col. 1).

The natural deoxynucleotides, which are the building blocks of DNA, include dATP, dGTP, dCTP and dTTP. Next, free pyrophosphate (PPi) produced in the RT-catalyzed reaction is converted to ATP by ATP sulfurylase (Id.). Finally, the ATP is measured in a luciferase assay and a light signal is emitted. The natural substrate for luciferase is ATP. However, the Karamohamed authors recognized that luciferase also recognized dATP as a substrate, and that use of dATP in the assay interfered with the luciferase reaction. To remedy this problem, the authors substituted a dATP analog, termed dATPαS, in place of dATP. The dATPαS was effectively incorporated by the DNA polymerase (RT), but was not recognized by the luciferase (Karamohamed at p.305 col.4).

The RdRp assay of the present invention also relies on detection of ATP by luciferase. When considering the modifications that would need to be made to the Karamohamed method in order to detect the activity of an RNA polymerase, one skilled in the art would immediately recognize a problem. In order to build RNA, the riboforms of the NTPs would have to be used in the assay. More specifically, ATP would need to be used in place of dATP, the deoxyriboform. As evidenced in Moyer et al., Anal. Biochem 131:187-189 (1983) (hereinafter Moyer, copy attached), ATP is greater than 50-fold more active than dATP as a luciferase substrate. There simply would have been no way to predict whether the modifications the authors of Karamohamed made to dATP would have been effective with the much more active ATP in an RdRp assay. And without knowing wither an ATP analog could serve as a substrate for RdRp in the polymerase reaction without interfering with the luciferase assay, one skill in the art would not have considered the presently claimed methods to be obvious.

Not until the present invention was there any reason to expect that ATPαS would be an effective substitute for ATP in a luciferase assay. The present

specification (p.42, lines 18-22 and Figure 5b) reports the results of a control study conducted by the inventors in which the polymerization was prevented by omission of primer from the reaction mixture. As evidenced in Figure 5b, there was very little light emission in the absence of polymerization, indicating that ATPαS is not a strong substrate for luciferase. Not until this discovery was made by the present inventors, therefore, was an effective RdRp luciferase assay available to the public.

In summary, the combined teachings of Karamohamed, Lohmann and Moyer make clear that it would not have been obvious to adapt the assay in Karamohamed to detect the activity of an RdRp such as that disclosed in Lohmann. Applicants respectfully request that the rejections under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

For the reasons stated above, Applicants respectfully submit that amended claims 1-3, 7-14 and 18-22 are free of the prior art. Withdrawal of the rejections under U.S.C. § 102 and 103 is deemed appropriate and respectfully requested.

If the undersigned can be of assistance to the Examiner, please contact the undersigned at the number set forth below.

Respectfully submitted,

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